

***Evaluation of Cystic Salivary Gland Lesions by Fine-Needle Aspiration:
An Analysis of 21 Cases***

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**Evaluation of Cystic Salivary Gland Lesions by
Fine-Needle Aspiration: An Analysis of 21 Cases**

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Abstract:

Objective: To analyze the potential sources of diagnostic errors and overall accuracy rate of the fine needle aspiration biopsy (FNAB) diagnosis of cystic salivary gland neoplasms.

Study Design: A 10-year (1993-2002) retrospective review of the cytopathology slides from the Department of Pathology, Division of Cytopathology at Long Island Jewish Medical Center, New Hyde Park, NY, identified a total of 97 consecutive salivary gland FNAB cases that microscopically were interpreted as representing cystic lesions. Of these, 21 cases had histologic follow up at our institution.

Results: A correct diagnosis was rendered by FNAB in 15/21 (72%) cases. This included 9 Warthin's tumors, 2 mucoepidermoid carcinomas, 2 simple cysts, 1 cystadenoma and 1 abscess. Clinically insignificant discrepancies were identified in 3 of 21 (14%) FNABs. Clinically significant misdiagnoses were identified in a further 3 of 21 (14%) cases.

Conclusions: A systematic approach to the diagnosis of cystic salivary gland lesions by FNAB can result in a correct diagnosis in greater than 70% of cases. Careful attention should be directed at identifying the extracellular fluid component(s) present (mucoid vs. watery proteinaceous) as well as the predominant cellular component (e.g. lymphocytes, histiocytes, epithelial cells and oncocytes). It is important to recognize, however, that occasionally epithelial cells may not be detected on FNAB of cystic salivary gland lesions, either as a result of cellular dilution by cyst fluid or due to inadequate sampling. However, with all FNABs

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tentatively diagnosed as a mucinous cystic lesion, the referring clinician should be informed that a low-grade mucoepidermoid cannot be ruled out.

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Introduction:

Fine-needle aspiration biopsy (FNAB) is a useful pre-operative technique for the evaluation of patients with a salivary gland lesion^{1,2}. Judiciously applied, FNAB can assist the clinician in developing a suitable treatment plan. An accurate FNAB diagnosis of “non-neoplastic” or “benign neoplasm” can obviate the need for surgical intervention (e.g. a diagnosis of Warthin’s tumor in an older individual or high risk surgical candidate). FNAB can also be useful in confirming suspected recurrences of previously diagnosed malignant neoplasms, allowing for the implementation of palliative treatment.

Potential drawbacks with FNAB of the salivary glands are minimal. However, the pathologist should be aware of reports of worrisome histologic changes in benign parotid lesions attributed to pre-operative fine-needle aspiration, ranging from squamous metaplasia to necrosis and stromal hyalinization³.

A wide variety of developmental, non-neoplastic and neoplastic salivary gland lesions can present with a predominant cystic architecture (Table 1). Smears from these cystic lesions are frequently of low cellularity, primarily yielding a background of watery or mucoid fluid. This can make cytologic diagnosis exceedingly difficult.

The goal of this study was to review our experience at Long Island Jewish Medical Center with the FNAB diagnosis of cystic salivary gland neoplasms.

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Materials and Methods:

A retrospective review of the files from the Department of Pathology, Division of Cytopathology at Long Island Jewish Medical Center over a 10-year period (1993-2002) revealed a total of 97 consecutive cases of salivary gland FNABs that microscopically had a pattern suggestive of a cystic salivary gland lesion. In all cases, both air-dried smears stained by a modified Romanowsky technique (Diff-Quik™) and alcohol-fixed smears stained according to the Papanicolaou method were available for review.

Twenty-one cases, 20 of which presented in the parotid gland, had histologic confirmation. The hematoxylin and eosin-stained slides of these 21 cases with histologic follow up were independently reviewed by two pathologists (PW, PE) and agreement was reached on all cases included in this study using accepted criteria⁴. Cytohistologic comparison was performed by an experienced cytopathologist (PW). Particular attention was directed towards identifying the potential sources of diagnostic errors and correlating them with the histologic findings of the surgical specimens.

Results:

A total of 97 FNAB cases that grossly or microscopically had a cystic pattern were identified over a 10-year period. Seventy-six cases had no histologic follow up at our institution. While this number would appear to be high, a number of these patients did undergo surgical excision at other institutions. The FNAB diagnoses in those cases without histologic follow-up were: 42 Warthin's tumors, 25 cysts, 3

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benign lymphoepithelial lesions, 2 pleomorphic adenomas with cystic degeneration, 1 mucoepidermoid carcinoma, 1 “hemorrhagic cystic structure”, 1 intraparotid lymph node with cystification, and 1 “Warthin’s tumor versus benign lymphoepithelial lesion”.

Twenty-one cystic FNABs were identified that had histologic confirmation. A correct diagnosis was rendered by FNAB in 15/21 (72%) cases. This included 9 Warthin’s tumors, 2 mucoepidermoid carcinomas, 2 cysts, 1 cystadenoma and 1 abscess.

The majority of aspirates from the Warthin’s tumors yielded smears of variable cellularity containing a mix of oncocytic epithelial cells and small lymphocytes in a dirty, proteinaceous to watery background (Figures 1a, 1b).

Clinically unimportant discrepancies were identified in 3 of 21 (14%) FNABs. Two Warthin’s tumors were interpreted as cysts by FNAB. In both cases, the smears were sparsely cellular, with rare macrophages and lymphocytes in a background of amorphous proteinaceous material. No oncocytes were present. Epithelial cells were not identified, precluding an accurate determination of the nature of the cyst. In the third case, a benign lymphoepithelial lesion was interpreted as a plain cyst by FNAB. In this case, the smear consisted of aggregates of reactive lymphocytes, histiocytes, macrophages and lymphoid tangles.

Clinically significant misdiagnoses were noted in 3 of 21 (14%) FNABs. In one case diagnosed on FNAB as Warthin’s tumor with cystic changes (Figures 2a, 2b), scant populations of round epithelial cells, which might have raised the possibility of a mucoepidermoid carcinoma, were overlooked.

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In the second case (Figures 3a, 3b), a papillary cystic neoplasm, which was ultimately interpreted as consistent with a low-grade adenocarcinoma, was called an oncocytic neoplasm with cystic change on FNAB. The FNAB differential diagnosis included oncocytoma and Warthin's tumor, with the latter favored. The smears consisted of cohesive clusters of oncocytic cells, some of which had a granulated cytoplasm, and mild atypia. Rare mitoses were noted. The background consisted of numerous foamy macrophages. Lymphocytes were not identified. The differential diagnosis included oncocytoma and Warthin's tumor, with the latter favored. Due to the somewhat ambiguous FNAB presentation, the need for careful clinical-pathological correlation was recommended. The intraoperative pathology consult was interpreted as representing a ruptured cyst, partially lined by squamous cells. Final diagnosis was deferred to the permanent section. Even on permanents, this proved to be a difficult diagnosis. Ultimately, following extensive intradepartmental debate and outside consultation, a diagnosis of papillary cystic neoplasm, consistent with a low-grade adenocarcinoma was rendered.

In the third case, the FNAB smear was composed of rare benign ductal cells, some with squamous metaplastic changes, in a background of proteinaceous, mucinous and degenerated amorphous material. On FNAB, this was believed to most likely represent a benign, non-neoplastic epithelial cystic lesion such as a retention cyst. However, following consultation with the treating surgeon, the differential diagnosis was revised to include the possibility of a low-grade mucoepidermoid carcinoma, myxoid degeneration in a pleomorphic adenoma, or salivary duct carcinoma, with the proviso that more definitive evaluation was

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precluded due to scant cellularity. On histologic evaluation, the initial FNAB diagnosis turned out to be correct. The final histologic diagnosis was sclerosing sialoadenitis with marked ductal ectasia, cyst formation and lymphoid aggregates.

One additional case (Figures 4a, 4b) illustrates the limitations imposed by sampling. FNAB of this parotid lesion revealed mucinous material containing normal ductal epithelial cells, macrophages and a mixed inflammatory infiltrate, consistent with a mucinous cystic lesion. Even on frozen section, a more definitive diagnosis proved problematic. On the final biopsy, only small areas of the specimen contained characteristic histologic features consistent with mucoepidermoid carcinoma.

Discussion:

A systematic approach to the diagnosis of cystic salivary gland lesions by FNAB can result in a correct diagnosis in 70-80% of cases. This should first involve determining the predominant fluid type; mucoid (mucoepidermoid carcinoma, mucous cyst, cystic pleomorphic adenoma, cystadenocarcinoma) versus watery proteinaceous (benign lymphoepithelial cyst, Warthin's tumor, cystadenoma, cystadenocarcinoma, polycystic disease of the parotid gland). Subsequent evaluation of the epithelial components, (e.g. lymphocytes, histiocytes, epithelial cells, oncocytic change) when present, often allows for the differential diagnosis to be further narrowed down. As with all FNABs, evaluation of the architecture of cell clusters is important.

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An FNAB consisting of a watery to stringy mucoid background containing large vacuolated mucin-rich epithelial cells and smaller basaloid intermediate cells strongly implies a diagnosis of a low-grade mucoepidermoid carcinoma.

A relatively acellular smear containing histiocytes and lymphocytes in the absence of epithelial cells is suggestive of a mucous cyst. However, it is important to recognize that occasionally, epithelial cells may not be detected, either as a result of cellular dilution by cyst fluid or due to inadequate sampling. Therefore, in this situation mucoepidermoid carcinoma cannot be entirely excluded and the referring clinician should be notified of this limitation.

Fragments of myxoid, chondroid material containing small clusters of myoepithelial and epithelial cells in a mucinous background are seen in FNABs from pleomorphic adenomas with a cystic architecture.

When examining a smear with the classic triad consisting of a dirty background of watery proteinaceous material and cellular debris, containing a mixed lymphocytic population and clusters of oncocytic epithelial cells, a diagnosis of Warthin's tumor can be rendered with confidence. The presence of oncocytes alone however is not diagnostic of Warthin's tumor since oncocytes are also seen in oncocytoma, obstruction, chronic sialoadenitis, pleomorphic adenomas and in the elderly.

When the lymphocytic infiltrate is heavy (primarily small mature lymphocytes), and a moderate to low number of non-oncocytic cuboidal to columnar epithelial cells are seen, a benign lymphoepithelial cyst is suggested⁵. The epithelial cells may have a mucinous, foamy, or granular appearance. It is not uncommon to also see the

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occasional tingible-body macrophages. In cases of multiple benign lymphoepithelial cysts, clinical examination will reveal a mass of doughy consistency. The patient will often have a history of HIV-associated immunosuppression.

FNABs of cystadenomas render smears composed of bland epithelial cells in a watery proteinaceous background, occasionally arranged in a papillary configuration. An occasional atypical squamous element can also be seen.

Polycystic (dysgenetic) disease of the parotid is a rare developmental condition of the parotid gland characterized by recurrent, painless swelling of the involved gland. Histologically, the overall architecture of the gland is preserved, but the salivary lobules are markedly distended by multiple epithelial-lined cysts. FNAB reveals a scant lymphoid infiltrate and rare clusters of bland columnar to cuboidal epithelial cells in a bloody or clean background.

Papillary cystadenocarcinomas are characterized by the presence of tissue fragments with a three-dimensional papillary configuration composed of cytologically atypical cells. The cyst contents can consist of either a mucoid or proteinaceous watery fluid.

Our accuracy rate for the FNAB diagnosis of cystic salivary gland lesions compared favorably with those of Layfield and Gopez⁶. We noted an accuracy rate of 72% (15/21), with a “significant error” rate of 14% (3/21). This compares to an accuracy rate of 84%, and a “significant error” rate of 9% reported by Layfield and Gopez when examining 56 FNAB cases over an 18-year period at the University of Utah Medical Center. Of the 3/21 “significant” misdiagnoses, one had been initially

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diagnosed correctly by FNAB, but the differential diagnosis was amended following consultation with the referring surgeon. The second “significant” misdiagnosis involved an oncocytic neoplasm with cystic change. However, even on permanents this proved to be a difficult diagnosis (papillary cystic neoplasm, consistent with a low-grade adenocarcinoma).

One well-recognized potential error, the misinterpretation of nests of atypical metaplastic cells from Warthin's tumors as representing a squamous cell carcinoma⁷, was not noted in this series.

Another well-recognized potential pitfall with the FNAB of cystic salivary gland lesions is related to the fact that the cyst fluid often dilutes the number of cells available for diagnosis. One of the most error-prone and potentially most clinically significant FNABs diagnoses is seen in cases of mucoepidermoid carcinoma⁸. Kupar et al⁹ reported a diagnostic accuracy of less than 50% by FNAB. According to Cohen et al¹⁰ the presence of overlapping epithelial groups, mucin-containing cells, and intermediate cells afforded specificity of 100%, sensitivity of 97%, yielding only 1 false negative of 96 cases examined. However, often all three cell types are not present in the sample examined (Figures 4a, 4b).

The FNAB differential diagnosis of mucoepidermoid carcinomas includes: mucous retention cyst, Warthin's tumor, branchial cleft cyst, benign lymphoepithelial lesion, chronic obstructive sialoadenitis, and necrotizing sialoadenitis. Fluid obtained from Warthin's tumors, mucoepidermoid carcinomas and non-neoplastic cysts may be very similar. Aspirates of low-grade mucoepidermoid carcinoma may contain no epithelial cells, resulting in a false-negative diagnosis of retention cyst. In fact, some

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very well differentiated mucoepidermoid carcinomas may be indistinguishable from mucus retention cysts by FNAB. Moreover, squamous metaplasia in a mucoid background in Warthin's tumor can readily be misinterpreted as mucoepidermoid carcinoma, resulting in a false-positive diagnosis of mucoepidermoid carcinoma.

In our institution, the majority of the FNABs for which surgical follow up could not be determined had been identified as Warthin's tumor (42/76) or salivary cyst (25/76). This emphasizes the importance of trying to avoid this misdiagnosis, since in some cases an FNAB diagnosis of Warthin's tumor or salivary cyst may lull the clinician into a false sense of security. It is also important to recognize that occasionally, the cytologic features required for a correct diagnosis are missing, either as a result of cellular dilution by cyst fluid or due to inadequate sampling. Based on our observations, we agree with the recommendations of Layfield and Gopez⁶ that in all FNAB cases diagnosed as mucous cyst, the possibility of a well-differentiated mucoepidermoid carcinoma should be considered. The referring clinician should be informed that although the FNAB is suggestive of mucous retention cyst, a low-grade mucoepidermoid cannot be excluded.

Conclusions:

A retrospective review of 21 consecutive FNABs of cystic salivary gland neoplasms with histologic follow-up at our institution over a 10-year period identified an FNAB accuracy rate of 72% (15/21), with a "significant error" rate of 14% (3/21). These findings confirm that a systematic approach, coupled with an awareness of the common pitfalls in the diagnosis of cystic salivary gland lesions by FNAB, can

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result in a correct diagnosis in the majority of cases. However, it must be emphasized that with all FNAB cases tentatively diagnosed as mucous cyst, the possibility of a well-differentiated mucoepidermoid carcinoma should be considered. The referring clinician should be informed that although the FNAB is suggestive of mucous retention cyst, a low-grade mucoepidermoid cannot be excluded.

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**Table 1: Lesions of the Salivary Glands with a Predominantly Cystic
Architecture**

Developmental:

- Polycystic disease of the salivary gland

Non-neoplastic:

- Mucous retention cyst
- Lymphoepithelial cyst

Benign neoplasms:

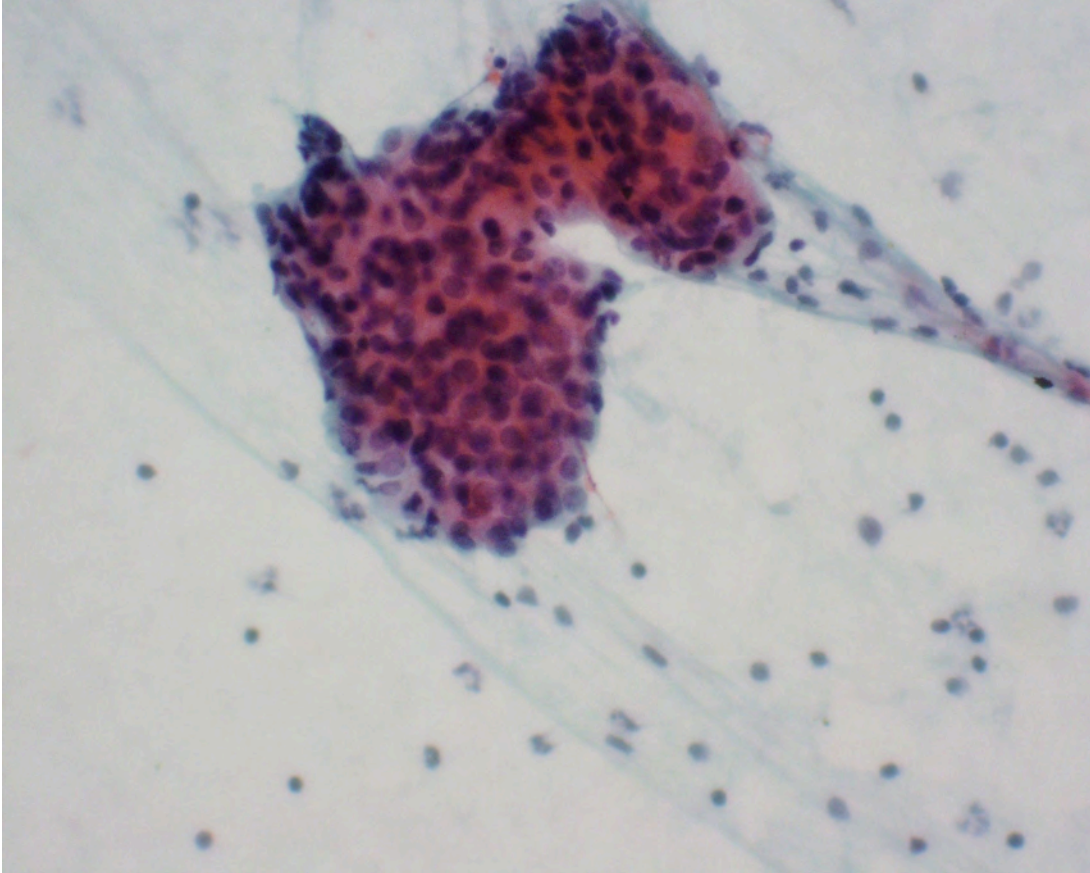
- Warthin's tumor
- Cystadenoma
- Cystic pleomorphic adenoma

Malignant neoplasms

- Mucoepidermoid carcinoma, low grade
- Cystadenocarcinoma

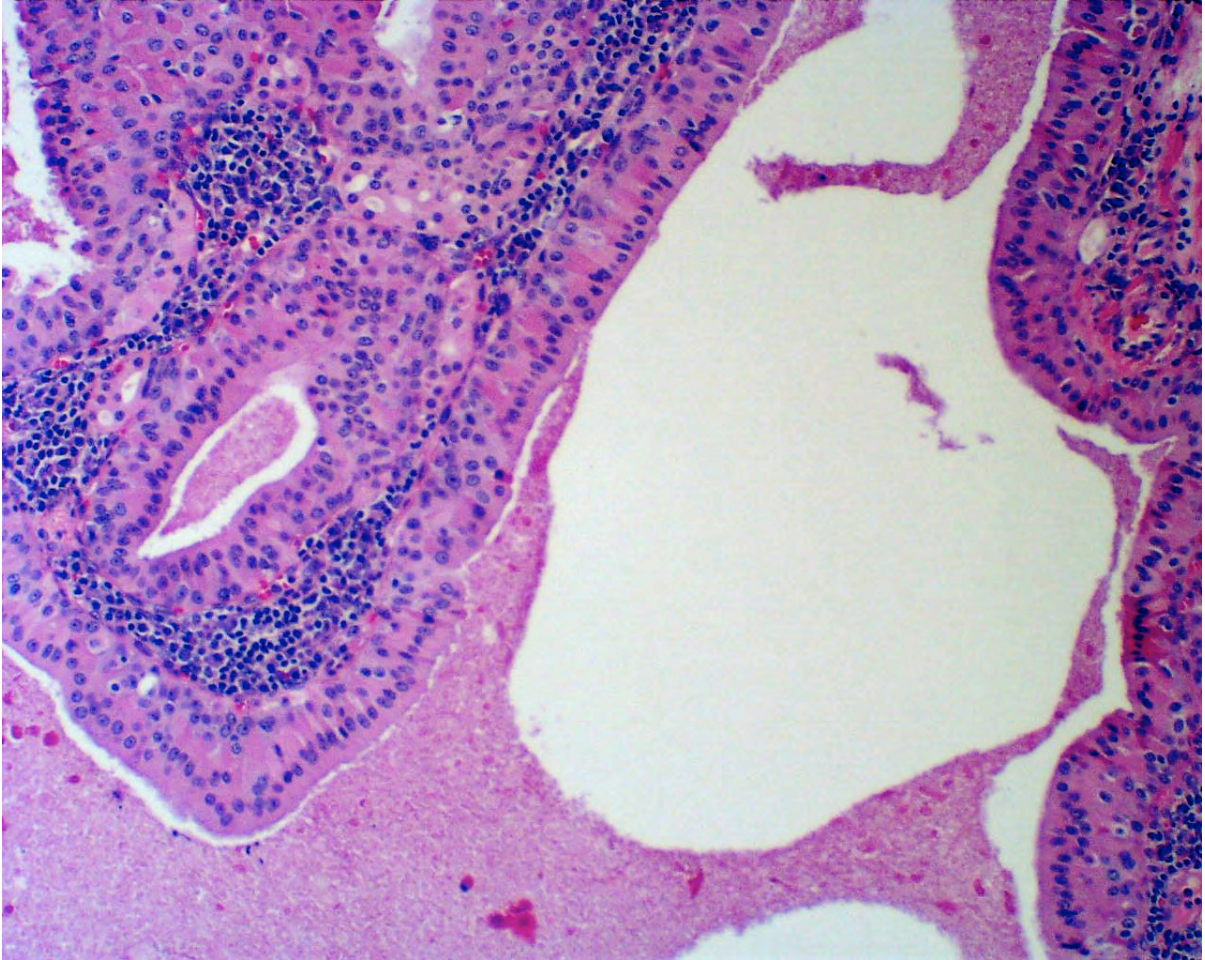
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Figure 1a: Aspirate specimen from a case of Warthin's tumor of the parotid gland. Sheets of oncocytes are present in a dirty, proteinaceous background containing small lymphocytes and rare neutrophils (Papanicolaou stain, original magnification 100x).



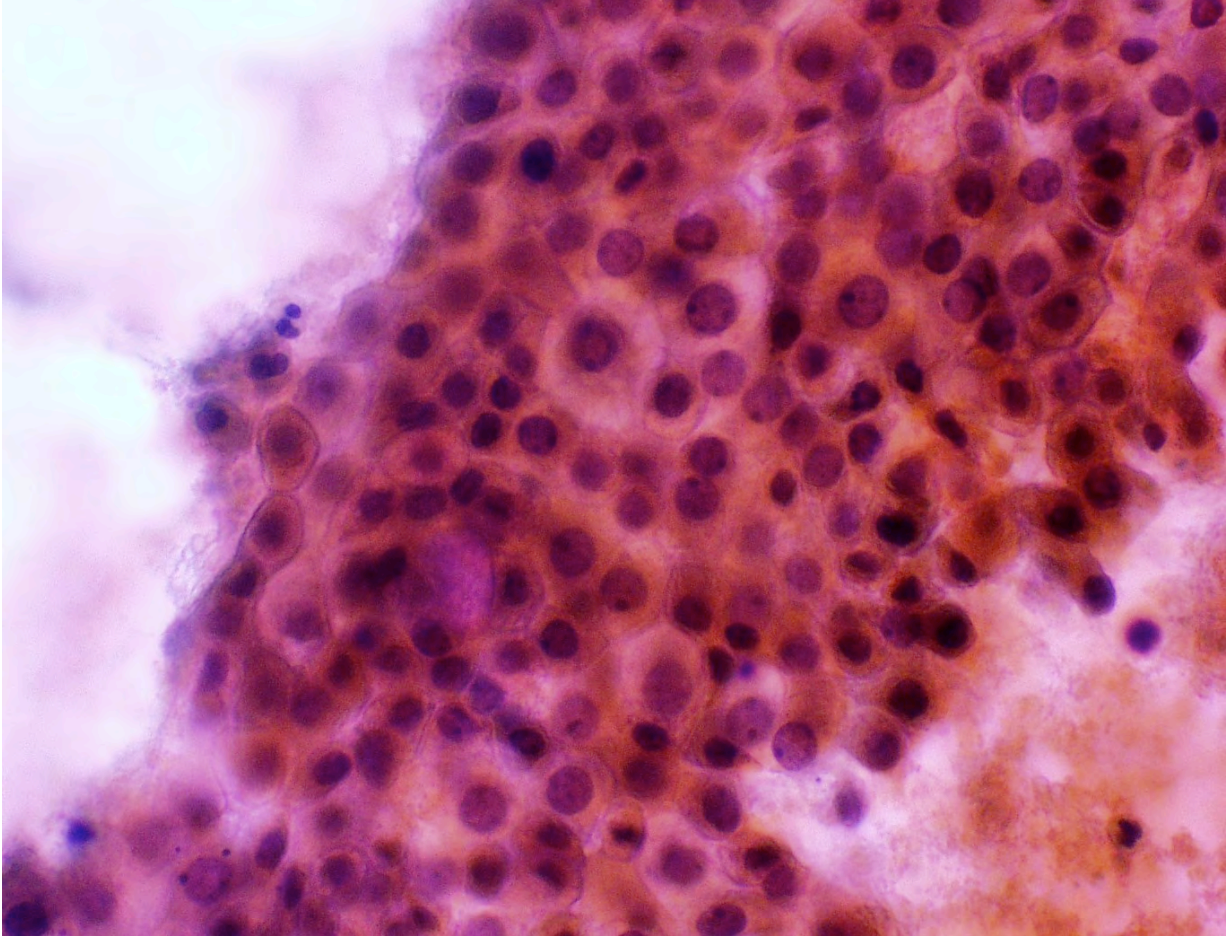
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Figure 1b: Histologic section of Warthin's tumor showing cystic space lined by double row of oncocytes bordered by lymphoid tissue (Hematoxylin and eosin, original magnification 50x).



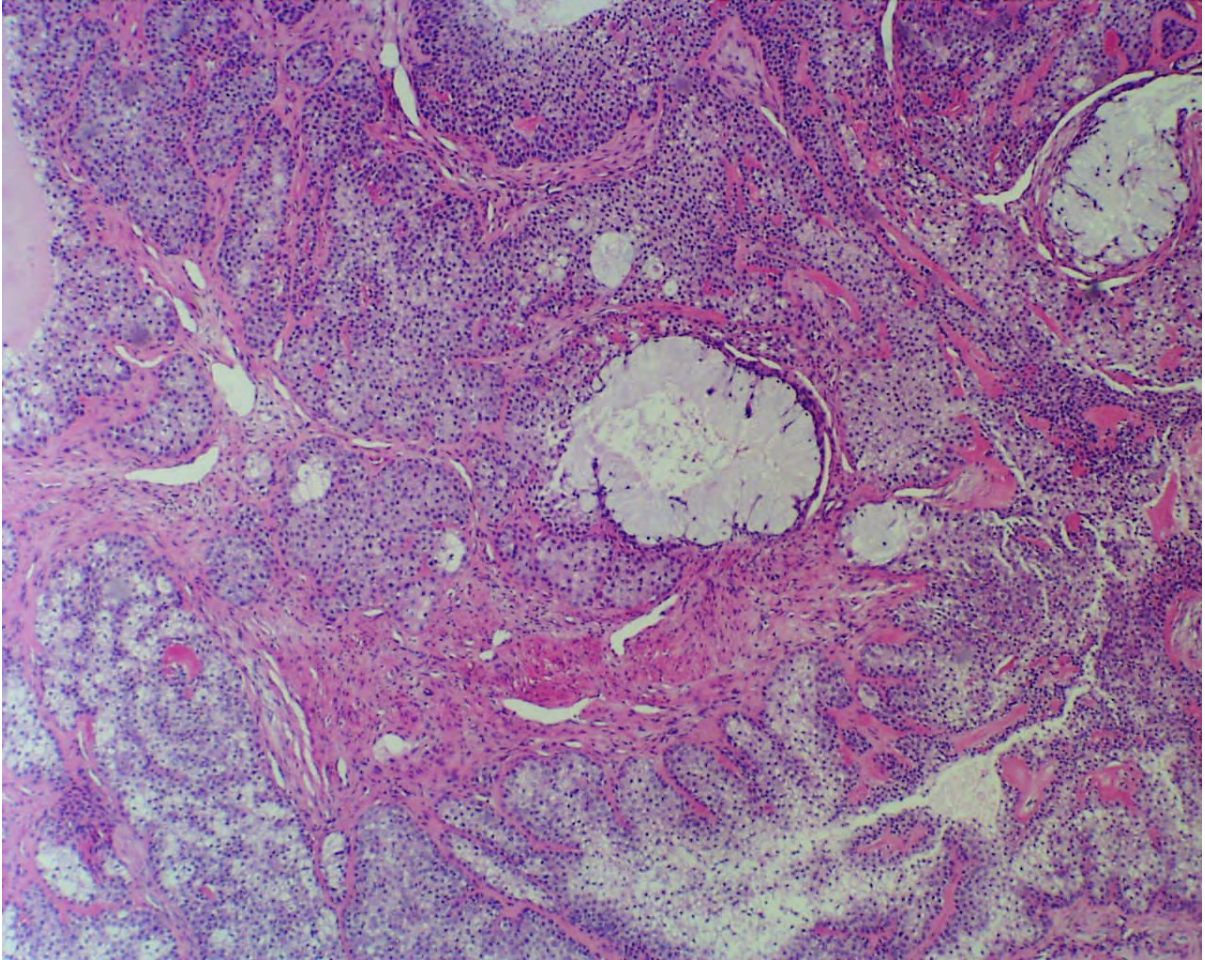
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Figure 2a: Aspirate specimen from a case of mucoepidermoid carcinoma of the parotid gland that was interpreted as a Warthin's tumor on FNAB. The smear shows groups of uniform, round epithelial cells with abundant clear cytoplasm and distinct cytoplasmic borders. (Papanicolaou stain, original magnification 100x).



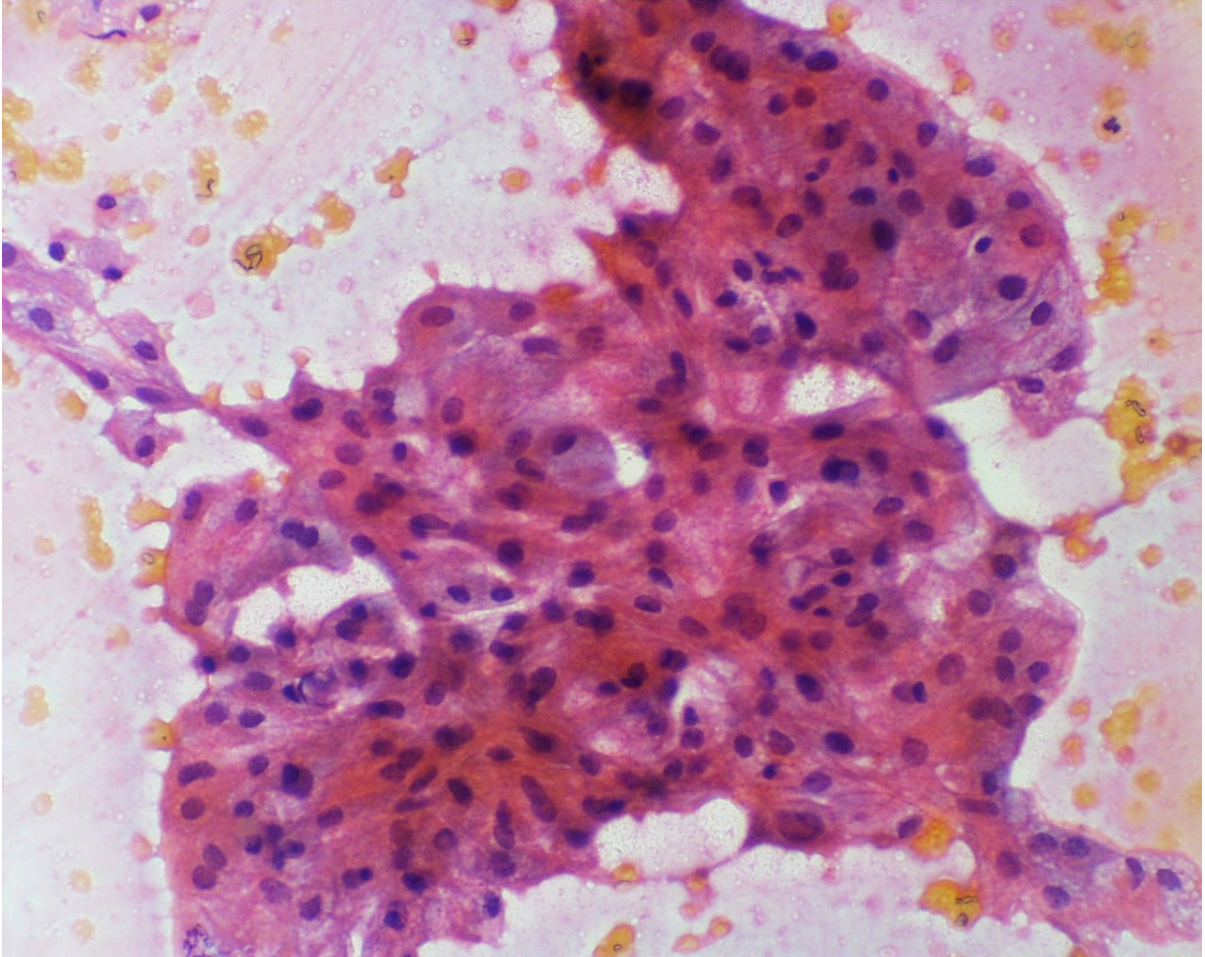
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Figure 2b: Histologic section of mucoepidermoid carcinoma of the parotid gland demonstrating a predominance of intermediate squamoid cells and mucous cells (Hematoxylin and eosin, original magnification 50x).



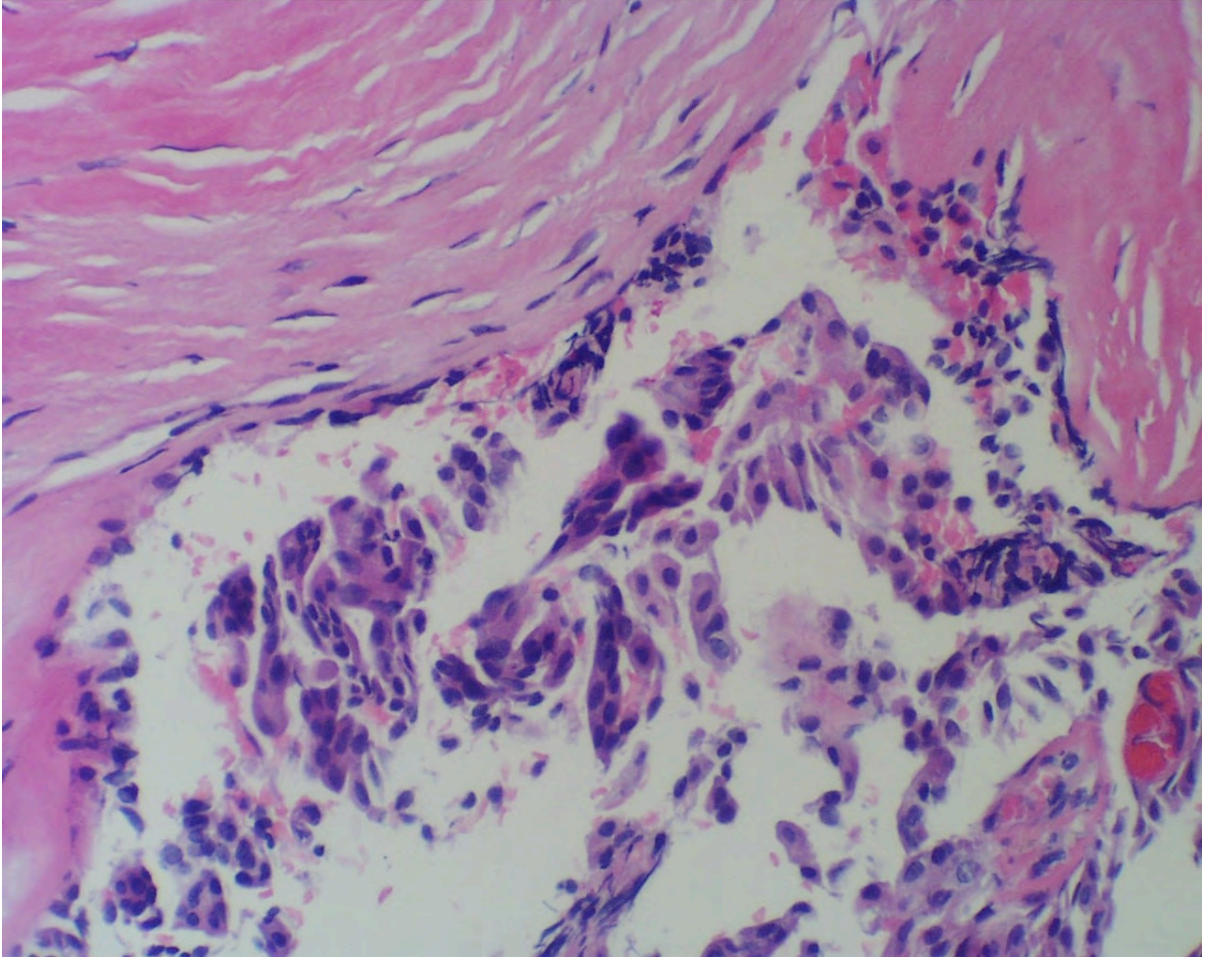
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Figure 3a: Aspirate specimen believed to represent an “oncocytic neoplasm with cystic change” on FNAB. The smear consists of cohesive clusters of oncocytic-appearing cells, some with abundant basophilic and granulated cytoplasm and mild atypia. Rare mitoses were noted. The background consisted of numerous foamy macrophages. Lymphocytes were not identified. The differential diagnosis included oncocytoma and Warthin’s tumor, with the latter favored. In retrospect, the possibility of an acinic cell carcinoma could also have been considered (Papanicolaou stain, original magnification 100x).



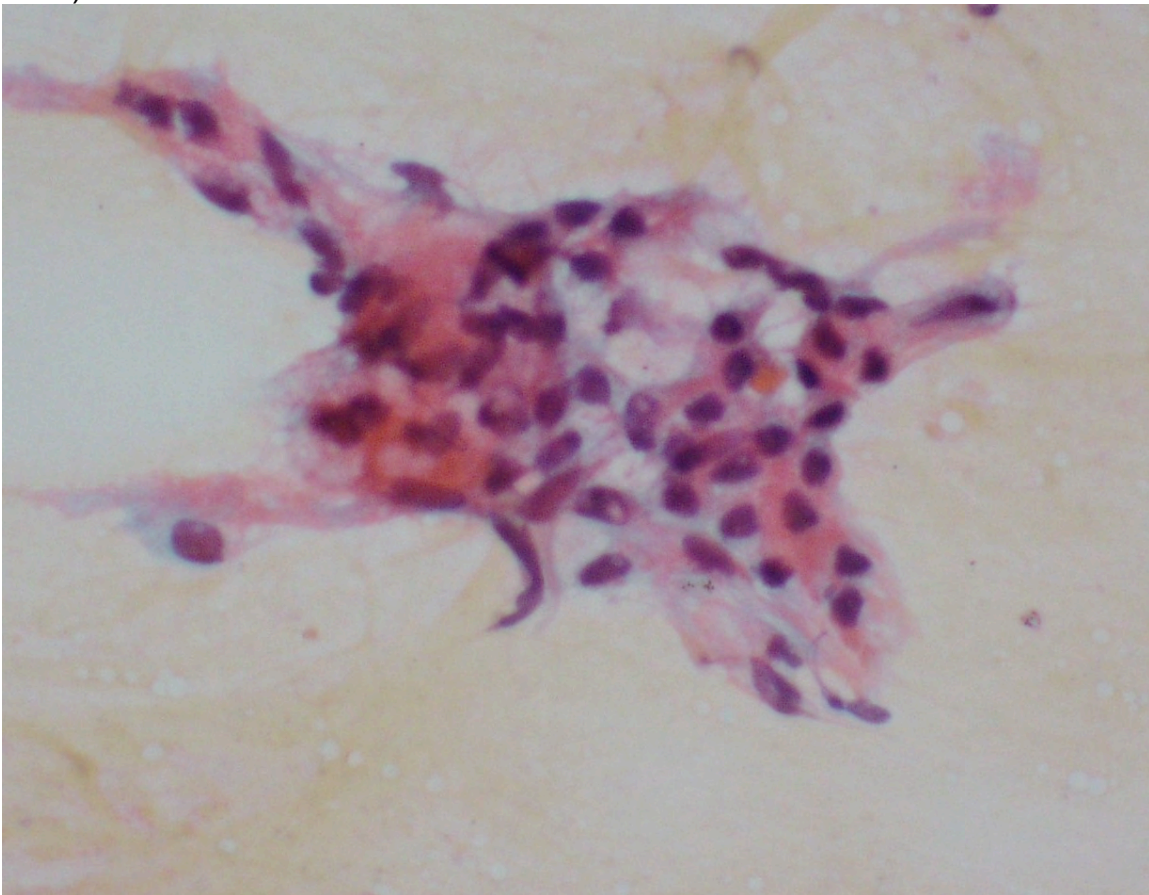
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Figure 3b: Histologic section of a papillary cystic neoplasm of the parotid gland consistent with low-grade adenocarcinoma. A collagenous stroma, focally lined by large eosinophilic cells is evident. Some atypia is also noted. (Hematoxylin and eosin, original magnification 100x).



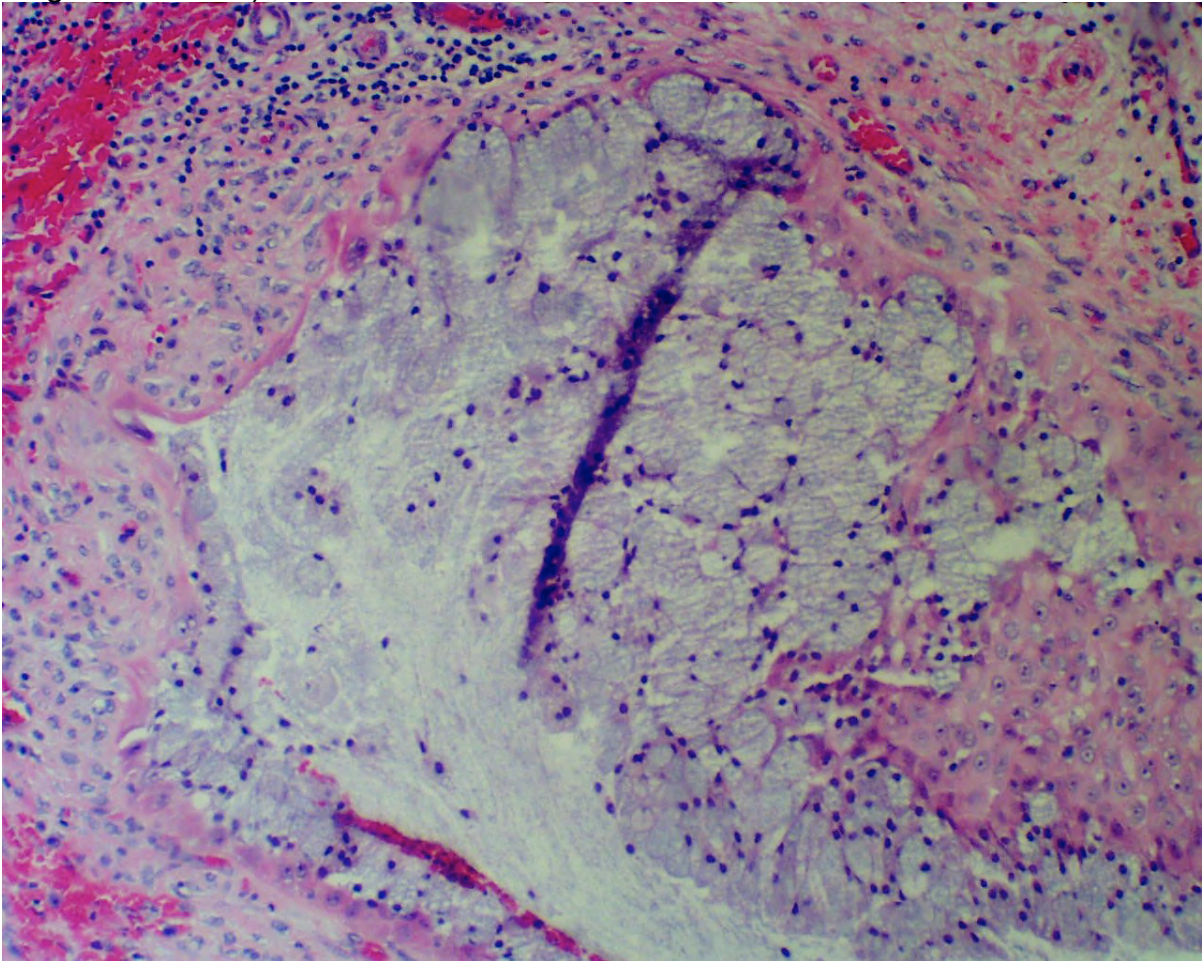
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Figure 4a: Aspirate specimen from a case of mucoepidermoid carcinoma of the parotid gland illustrating limitations imposed by sampling. FNAB revealed abundant mucinous material containing aggregates of normal ductal epithelial cells, rare macrophages and mixed inflammatory cells. This was interpreted as being consistent with a mucinous cystic lesion (Papanicolaou stain, original magnification 100x).



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Figure 4b: Histologic section of mucoepidermoid carcinoma showing a predominance of mucous cells. Only small areas of the specimen contained this characteristic histology. On frozen section, because of sampling limitations, the typical histologic features of mucoepidermoid carcinoma were not seen. A mucinous cystic tumor was favored, with the observation that well-differentiated mucoepidermoid carcinoma could not be excluded (Hematoxylin and eosin, original magnification 50x).



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